IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S.-Au, *et al.*
Serial No.	:	10/807,620
Filed:	:	March 24, 2004
For:	:	Methods And Compositions To Determine The Chemosensitizing Dose Of Suramin Used In Combination Therapy
TC/AU	:	1614
Examiner	:	James D. Anderson
Attorney Docket No.	:	TNI 2-011

BOARD OF PATENT APPEALS AND INTERFERENCES
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

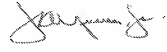
APPELLANTS' BRIEF ON APPEAL

Sir:

Responsive to a Communication mailed April 19, 2010, submitted herewith is Appellant's Brief on Appeal as prescribed in 37 C.F.R. § 41.31. Reversal of the primary examiner's rejection of the appealed claims and their allowance is respectfully requested.

The requisite fee of $250.00 as required in 37 C.F.R. § 1.17(c) is submitted herewith. Any additional payments that may be required should be charged to Deposit Account No. 13-4830.

Respectfully submitted,



Date: 7 October 2010

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Real Party in Interest

The appealed application has not been assigned; however, Optimum Therapeutics, LLC, an Ohio limited liability company, has commercial rights in the application.

Related Appeals and Interferences

There are no related appeals or interferences known to Appellants, their legal representatives, or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Twenty-six claims were submitted with the application as originally filed.

An Office Action was mailed on January 9, 2007 containing a three-way restriction requirement. In a response filed on February 6, 2007, Appellants elected the Group III claims 22-24, 26, and new claims 27-33. Claim 25 was canceled. All other claims were withdrawn from prosecution.

An Office Action was mailed on June 6, 2007 rejecting claims 22-24 and 26-33. Appellants filed a response on September 10, 2007, canceling claims 23, 24 and 29, and adding new claim 34.

An Office Action was mailed on December 12, 2007 rejecting claims 22, 26-28, and 30-34. Appellants filed a response on March 6, 2008, that included a declaration from co-inventor Dr. Jessie L.-S. Au.

An Advisory Action was mailed on April 9, 2008 entering the March 6, 2008 response with declaration, but maintaining the rejection of the claims.

Appellants filed a Pre-Appeal Brief Request for Review on June 17, 2008 with a Notice of Appeal. A Notice of Panel Decision From Pre-Appeal Brief Review was mailed on July 11, 2008 reopening prosecution, withdrawing the finality of the December 12, 2007 Office action, and deeming the Notice of Appeal Moot. Claims 22, 26-28, and 30-34 again were rejected. Appellants filed an amendment on October 15, 2008 amending claim 22 and canceling claim 31.

An Office Action was mailed on January 5, 2009 rejecting claims 22, 26-28, 30, and 32-34. Appellants filed a response on July 1, 2009.

A Notice of Appeal was filed on July 6, 2009.

An Advisory Action Before the Filing of an Appeal Brief was mailed on August 25, 2009, indicating that the response of July 1, 2009 will not be entered, maintaining rejection of claims 22, 26-28, 30, and 32-34.

An Appeal Brief was filed on August 26, 2009.

Appellants entered a Request for Continued Examination, and re-filed on August 31, 2009 the response previously filed on July 1. Claim 22 was amended.

An Office action was mailed on October 26, 2009, again rejecting claims 22, 26-28, 30, and 32-34.

Appellants filed a response on February 18, 2010, canceling claims 22, 26, 30, and 34; amending claims 27, 28, 32, and 33; and adding new claim 35.

An Office action was mailed on April 19, 2010, rejecting claims 27, 28, 32, 33, and 35 in a final rejection.

Appellants filed a Pre-Appeal Brief Request for Review on July 20, 2010.

A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on September 7, 2010, concluding that at least one actual issue for appeal existed.

The instant Brief on Appeal was filed 7 October 2010.

Status of Amendments

All of the amendments submitted by Appellants have been entered.

Summary of the Claimed Subject Matter

The claims are directed to a kit for carrying out the administration of non-cytotoxic suramin as a sensitizer in a patient (see claim 35). In particular, the kit includes suramin in a pharmaceutical carrier, and instructions for the use of said suramin as a sensitizer.

The printed instructions are required to enable the calculation of personalized non-cytotoxic suramin dose for a patient. The instructions include the steps of using certain patient-specific information to calculate the required dose of suramin for an individual patient, in order to achieve the desired low and non-cytotoxic circulating suramin concentrations of below 200 μM. The need of maintaining such concentrations is because Appellants have demonstrated that the therapeutic use of suramin as a sensitizer can only be achieved at such non-cytotoxic levels and not at higher cytotoxic levels (see specifications at p. 5 l. 22 bridging p. 6 l. 7). This dose-response relationship is highly unusual and contradicts the general expectation that a higher dose produces a higher response rather than abolishing the response. Due to this unusual dose-response, a physician or a pharmacist must have the means to determine the suramin dose that would yield non-cytotoxic concentrations without risking attaining the higher concentrations.

The printed instructions represent new and unobvious findings that cannot be anticipated based on the art regarding dose-calculation of cytotoxic suramin or other drugs. For most drugs used in human patients, choosing the proper dose is a relatively routine and an easy task. For example, most chemotherapy agents are given at a fixed frequency and at a fixed dose, because most agents have plasma half-lives of several hours and are eliminated from the body within days and, therefore, will not show significant accumulation in the body by the time the next dose is administered, usually in 7 or 21 days. However, as discussed in the specification, this general practice does not apply to non-cytotoxic suramin (see specifications at p. 4 ll. 18-31, p. 21 ll. 11-12, and p. 31 ll. 20-26). This is true in part because non-cytotoxic suramin displays several unique pharmacokinetic properties in human patients, such that the calculation of the non-cytotoxic suramin dose cannot be performed using the methods in the art. First, the disposition of low and non-cytotoxic doses of suramin in patients shows a substantial inter-subject variability (180%), indicating that the same dose of suramin will not result in the same, desired plasma concentration in all patients. In fact, different patients require doses of up to 5-fold different size. Second, suramin has an unusually slow elimination from the body with a half-life of about 10 days, indicating that a significant residual amount will remain in the body at the time of the next treatment (*e.g.*, about 25% of the dose remaining in 20 days for a half-life of 10 days). Third, unexpected changes in treatment frequency or time intervals between treatment cycles are fairly common in cancer chemotherapy. These changes can be due to changes in

patients' health status or other circumstances, and will affect the amount of residual drug and, therefore, introduce uncertainty on deciding on the proper dose. If the dose in the subsequent treatment exceeds the amount that has been eliminated, drug accumulation will occur and will cause the plasma concentrations to increase, *e.g.*, to levels where suramin is not effective. Conversely, an insufficient dose will yield ineffective concentrations. Due to the above unexpected pharmacokinetic properties, the methods in the art for dose calculation for most drugs are not adequate. A new method or composition to take into account the various patient characteristics and the time interval between treatments, such that the patient is given the proper suramin dose, is absolutely required to enable the administration of non-cytotoxic suramin to patients.

In addition, as detailed in the specification (see p. 2 l. 19 through p. 6 l. 15), Appellants, after conducting extensive studies in human patients, discovered that the methods in the art that were used to administer cytotoxic suramin cannot be applied to non-cytotoxic suramin. This is because of the numerous differences of the elimination between non-cytotoxic suramin and cytotoxic suramin. For example, the overall elimination of non-cytotoxic suramin is more rapid relative to cytotoxic suramin. The renal elimination is insignificant for non-cytotoxic suramin (*e.g.*, 10%) but is the major pathway for eliminating cytotoxic suramin. Another cause is the vastly different concentration requirements for the two uses of suramin, *i.e.*, *inter alia*, the high and toxic levels sustained for up to 45 weeks for suramin used as a cytotoxic agent and the low and non-cytotoxic levels for a much shorter duration of 2 days for suramin used as a sensitizer. One method for administering cytotoxic suramin is to use measurement of actual plasma concentrations, which is highly labor-intensive, costly, and not available to the general public. The second method of fixed dosing schedules, designed to maintain constant and high cytotoxic concentrations of suramin over long treatment durations of more than two months, is not applicable to the use of non-cytotoxic suramin as a sensitizer in view of the differences in pharmacokinetics, as discussed above. Further, these fixed dosing schedules were derived from studies in male patients with prostate cancer and may not be suitable for a mixed-gender population in view of Appellants' unexpected finding of a gender-related difference in the pharmacokinetics of non-cytotoxic suramin. In addition, the art on dose calculation of cytotoxic suramin does not offer provisions for deviations or changes in the planned treatment schedule or frequency. The dosing schedules of cytotoxic suramin are based on the body surface area (BSA) whereas Appellants found that calculation of personalized non-cytotoxic suramin dose requires using the squared value of BSA. Appellants respectfully draw the Court's attention to the many additional differences between the art on cytotoxic suramin and the instant disclosure,

outlined under "Argument" in the section with the heading of "Examiner's statements 5 and 8 relate to the prior art".

Finally, the inter-subject variability in suramin elimination is much greater for non-cytotoxic suramin than for cytotoxic suramin. These differences make it impossible to use the dose calculation methods for cytotoxic suramin to calculate the dose for non-cytotoxic suramin. The numerous differences in the disposition of cytotoxic suramin and non-cytotoxic suramin, together with the substantial (180%) inter-subject variability in the elimination of non-cytotoxic suramin and in view of the need of maintaining the circulating suramin concentration in a narrow range in order to achieve sensitization, mandate the development of a new method that is different and not based on the art for administering the cytotoxic suramin.

In short, the surprising findings of the unusual and unexpected pharmacokinetics of non-cytotoxic suramin in human patients, in view of the multiple sources of inter-patient variability mean that, absent the dosing nomogram in the instant disclosure, it will be impossible to predict how an individual patient will react to the administered dose of the suramin.

Development of the printed instructions required extensive experimentation and involved multiple unexpected discoveries. As stated in the declaration of Dr. Au, dated March 6, 2008, the development of an effective method of administering suramin required extensive research and development in human patients. Dr. Au is a co-inventor of the appealed application. She and her collaborators evaluated several methods. Initial studies used real time pharmacokinetics together with computer simulations to determine the correct dose. Real time pharmacokinetics means that blood samples were taken from patients to determine the plasma concentrations of suramin at a specific time, usually a day before the scheduled treatment, so as to enable the calculation of the drug dose needed to bring the concentrations to the desired level. These initial methods were found to be sufficient to yield and maintain the desired suramin concentrations for 48 hours. However, these methods can only be applied in a limited number of medical centers that have these highly specialized research capabilities and, therefore, are not applicable to the general public. In other words, the ability to use non-cytotoxic suramin as a sensitizer in patients relies on using the method of dose calculation or nomogram presented in the appealed application.

Appellants have developed the equations and the corresponding nomogram that enable the calculation of the requisite non-cytotoxic suramin dose. These equations, developed using the pharmacokinetic data of non-cytotoxic suramin obtained in human patients together with *in silico* analysis, has enabled the calculation of the required non-cytotoxic suramin dose such that 94% of the treatments administered to patients yielded circulating suramin concentration within the desired target range. This high level of success rate is especially impressive in view of the

substantial inter-patient variability (180%) in the disposition of suramin, which typically makes it difficult to find the right dose for individual patients.

The nomogram and the underlying equations disclosed in the appealed application are based on unusual parameters not encountered or used in the art. The nomogram provides a numerical value of a FACTOR with a fixed value for the first suramin treatment. Equation 16 and the nomogram provide the FACTOR value for the second and subsequent treatments based on the elapsed time in days since the initiation of the last suramin treatment. This FACTOR then is used together with the squared value of the body surface area of the patient to calculate the suramin dose for the first and subsequent treatments. As discussed throughout this brief, these equations and FACTOR are specific to the use of non-cytotoxic suramin as a sensitizer, and are not known in the art for calculating the dose of cytotoxic suramin or other drugs.

As indicated in the appealed application and in Appellants' publication (Chen, 2006), the development and validation of the nomogram method required extensive research, and yielded surprising and unexpected results that either cannot be anticipated from the art or contradicts the teachings from the use of cytotoxic suramin (see Dr. Au's declaration dated March 6, 2008). The nomogram development was a multi-step process, as stated in (Chen, 2006), page 1266: 2, last ¶:

> First, we used the pharmacokinetics results in the first cohort of six phase I patients to determine the duration that covered >90% of paclitaxel/carboplatin AUC, with the goal of maintaining the plasma suramin concentrations at between 10 and 50 μM over this duration. This led to adjustments in the suramin regimen; administering suramin in two split doses yielded the target concentrations over 48 hour in the second cohort of six patients. The pharmacokinetics results of these 12 patients were then used with PPK [population-based pharmacokinetic] analysis to derive suramin dosing equations, which were then used to predict the dose in three additional patients. Through retrospective and prospective analyses of the precision and accuracy of the PPK based dosing equations, a correction factor was identified and used to derive a dosing nomogram. The predictive power of the nomogram was evaluated in 47 phase II patients.

As described in the application (Example IV), during the PPK phase of the nomogram development, 10 potential covariates were evaluated. One of these was patient gender. The initial results in a small number of patients suggested that the dose was affected by patient gender. However, further evaluation in large numbers of patients indicated that the gender-related difference in dose requirement was relatively small and could be ignored as long as other variables are accounted for by the nomogram. Another potential covariate was creatinine clearance, which was expected to be strongly correlated with suramin clearance. This is because the art has shown renal elimination as the primary route of clearance of cytotoxic

suramin (Collins, *J. Clin. Pharmacol.*, 26, 22, 1986; Piscitelli, *Pharmacotherapy*, 17, 431, 1997). The view that creatinine, and accordingly renal clearance, is important for suramin is shared by other artisans. For example, Motzer, *et al.* ("Phase II Trial of Suramin in Patients with Advanced Renal Cell Carcinoma: Treatment Results, Pharmacokinetics, and Tumor Growth Factor Expression" *Cancer Res* **53**, 5775-5779, October 15, 1992) state on page 5776, column 1, Introduction: "The pharmacokinetics of suramin include ..... predominantly renal elimination, ...". It is, therefore, surprising that Appellants, upon evaluation in human patients, found that creatinine clearance was not a significant predictor of PPK parameters for the use of non-cytotoxic suramin as a sensitizer. Appellants investigated this apparent discrepancy in a study in 38 patients, and determined that the renal clearance of non-cytotoxic suramin in human patients was surprisingly low, accounting for only approximately 10% of the total clearance.

Another surprising finding was that body surface area (BSA) was a less accurate predictor of dose requirement than its squared value, BSA^2. This was surprising, because many anticancer agents including cytotoxic suramin are administered based on body surface area, while a dose requirement based on BSA^2 is unknown to Appellants and certainly extremely uncommon.

Appellants further devised new methodologies for some of the steps in the nomogram development process. For example, no established method was available to optimize accuracy of the predicted dose. Appellants accomplished this task by using computer simulations to identify the "ideal dose" that would give the precisely desired plasma concentration at 48 hours. A comparison of this "ideal dose" with the actual results in patients led to the introduction of a correction factor that improved the accuracy of the nomogram predictions by 12%. The above composite findings then were used to develop the suramin dosing nomogram. The innovativeness of the nomogram is indicated by its success in finding the proper suramin dose to maintain the desired plasma concentrations in 94% of treatments. This high success rate is surprising especially since the substantial inter-patient variability (180%) usually means that it will be impossible to predict how a patient will react to a suramin dose. This underscores the nomogram is a novel method that can account for the most critical variables in individual patients such that the dose of non-cytotoxic suramin can be personalized in accordance to the patient's characteristics. Absent the nomogram, a physician or a pharmacist will not be able to determine the proper suramin dose for a patient without undue burden of extensive experimentation (see Dr. Au's declaration dated March 6, 2008).

The above shows that extensive, additional research was necessary to overcome or correct the deficiencies or misunderstanding in the art, and to reveal the new, unexpected and unobvious requirements for finding the correct dose in individual patients. As pointed out in Dr.

Au's declaration dated March 6, 2008, the amount of work involved in the development and validation of the nomogram is far beyond the standard of obviousness and could not have been anticipated based on the art on cytotoxic suramin.

The printed instructions transform suramin from being a cytotoxic agent without therapeutic utility to a potentially useful sensitizer. As discussed in the appealed application, multiple investigators have evaluated suramin for its activity as a cytotoxic agent, given alone or in combination with other cytotoxic agents. These investigators have found limited benefits or significant toxicities such that further evaluation of suramin was discouraged (see p. 2 ll 19-24).

Hence, without a method to enable the administration of suramin to achieve the desired non-cytotoxic circulating concentrations, suramin will have no therapeutic utility. The nomogram disclosed in the instant application is a simple and practical way to calculate a personalized suramin dose in individual patients that will yield the circulating non-cytotoxic concentrations that produce sensitization. As such, the nomogram enables the use of suramin, which, in view of the general recommendation that suramin should not be used to treating human patients, in effect is transforming suramin from a compound with no therapeutic value to a potentially useful drug.

Claims. Claim 35 is directed to a kit that includes suramin (see p. 5, ll. 20-32); and instructions for use (see, generally, p. 30, l. 15 bridging p. 34, l. 8; and original claim 22, *et seq.*). The suramin dose in claim 27 is discussed generally in the application at p. 5, l. 20 bridging p. 6, l. 12; and original claim 2). The suramin dose range in claim 28 is discussed in the application also at p. 5, l. 22. The suramin dose range and time frame in claim 32 is discussed in the application also at p. 6, ll. 5-6 and 8-9. Claim 33 is directed to giving suramin in split doses (see p. 33, ll. 17-20).

Grounds of Rejection to be Reviewed on Appeal

Appealed claims 27, 28, 32, 33, and 35 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being obvious over Agyin (U.S. Patent No. 6,900,235), and further over Tu *et al.* (Clinical Cancer Research, May 1998, volume 4, pages 1193-1201) in view of Agyin, and over Klohs *et al.* (U.S. Patent No. 5,597,830) in view of Agyin.

In levying the final rejection of the appealed claims, the Examiner has stated, *inter alia*:

1. The claimed nomogram is not given patentable weight because it merely provides instructions for administering suramin to a subject. Appellants are claiming a product, not a method of treatment. (Emphasis in original)

   April 19, 2010 Office action, p. 3 third paragraph.

2. .... the contents of instructions provided in a kit are not given patentable weight in claims drawn to a product (i.e., kit). It matters not what the content of the instructions is. (Emphasis in original)

   April 19, 2010 Office action, p. 5 first paragraph.

3. In this case, the recited instructions (i.e., printed material) are not functionally related to the claimed kit (i.e., product) because the instructions do not determine what is present in the composition or how much suramin is present in the kit.

   And

4. One skilled in the art could readily administer any known therapeutic dose of suramin to treat cancer and does not require Applicant's instructions and nomogram to do so.

   April 19, 2010 Office action, p. 6 third paragraph.

5. Agyin et al. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22). (Emphasis in original)

   April 19, 2010 Office action, p. 8 fifth paragraph.

6. ... it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight.

   April 19, 2010 Office action, p. 15 second paragraph.

7. As the court stated in Ngai, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. ..."

   April 19, 2010 Office action, p. 16 first paragraph.

8. Klohs et al. ... Suramin is disclosed to be administered at doses from about 275 mg/m2 to about 1000 mg/m2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 µg/mL (i.e., about 70 µM to about 210 µM) (col. 2, lines 27-35).

   April 19, 2010 Office action, p. 11 fourth paragraph.

9. There is no support, either explicit or implicit, for the claimed amount of suramin. Nowhere do Applicants teach the claimed limitation of an amount of suramin "not substantially in excess of about 800 mg".

   April 19, 2010 Office action, p. 7 fourth paragraph.

Examiner's grounds for rejection are grouped according to the subject matters and the Appellants' basis for overcoming the rejections are discussed below.

Argument

Appellants respectfully disagree with the final rejection, for the following reasons.

Examiner's statements 1, 2, 3, 4, 6 and 7 relate to the functional relationship between the printed instructions (nomogram in the instant appeal) and the substrate (suramin in the instant appeal), the patentable weight of printed instructions, and new and obviousness of the printed instructions. The Examiner noted MPEP § 2112.01 and established case law that indicates the requirement of "new and unobvious functional relationship between the printed matter and the substrate".

Appellants' Response:

Patentable weight of printed instructions and new and unobvious functional relationship between the nomogram and the administration of non-cytotoxic suramin as a sensitizer. It is material error to ignore printed instructions in applying Section 103(a), even if the printed matter does not constitute patentable subject matter. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983), the Court states the following:

> As for the examiner's characterization of the indicia and legend as "unpatentable printed matter," we note that the examiner himself recognizes the fact that printed matter, in an article of manufacture claim, *can* be given "patentable weight." He did so in allowing claims. His characterization of printed matter as "unpatentable" is beside the point; no attempt is here being made to patent printed matter as such. [**13] The fact that printed matter *by itself* is not patentable subject matter, because non-statutory, is no reason for ignoring it when the claim is directed to a combination. Here there is a new and unobvious functional relationship between a measuring *receptable*, volumetric *indicia* thereon indicating volume in a certain ratio to actual volume, and a *legend* indicating the ratio, and in our judgment the appealed claims properly define this relationship. * * *

The same Court further states that printed matter has patentable significance if there exists any new and unobvious functional relationship between the printed matter and the composition of the kit. *In re Ngai*, 35 USPQ2d 1384 (Fed. Cir. 2004). The MPEP expressly recognizes the vitality of the *Gulack* decision at MPEP § 2112.01 by stating, *inter alia*: "III. ... [T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate."

The Examiner uses the following criteria as test of a functional relationship between the nomogram and suramin, *i.e.*, the instructions need to determine what is present in the composition; and, the instructions need to determine how much suramin is present in the kit. But no basis or source for this test was cited. MPEP 2112.01 (Composition, Product, and Apparatus Claims [R-3]) @ § III (Product claims – nonfunctional printed matter does not

distinguish claimed product from otherwise identical prior art product) refers to the court decision Re: Ngai, but does not indicate how one should decide on whether printed matter has a "functional" relationship to the substrate. Other cases (*e.g.*, U.S. Patent Application No. 09/563,817, Appeal 2007-1823 (Decided Jan. 28, 2008) (Michael C. Nehls, Brian Zambrowicz, and Arthur T. Sands, applicants), in their consideration of the functional relationship between printed matter and substrate, refer to the Ngai case, which in turn refers to the Gulack decision:

> In *Gulack*, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result.

In *re Ngai*, it is noted that the court did not allow the initial kit claim:

> 19. A kit for normalizing and amplifying an RNA population, said kit comprising instructions describing the method of claim 1 and a **premeasured portions of a reagent selected from the group consisting of:** oligo dT T7 biotinylated primer, T7 RNApolymerase, annealed biotinylated primers, streptavidin beads, polyadenyl transferase, reverse transcriptase, Rnase H, DNA pol I, buffers and nucleotides.

The court considered this "a kit that contained at least one of several reagents (*e.g.*, buffer) and instructions that described a process of using the reagents to amplify RNA." (*In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004) at 1337). The claim was rejected based on prior art that disclosed a kit containing buffer and instructions that described a different process. *Id.*

An amended form of this claim, however, was eventually issued as follows (U.S. Patent No. 6,982,143).

> 19. A kit for normalizing and amplifying an RNA population, said kit comprising instructions describing the method of claim 1 and a **premeasured portions of** oligo dT T7 biotinylated primer, T7 RNApolymerase, annealed biotinylated primers, streptavidin beads, polyadenyl transferase, reverse transcriptase, Rnase H, DNA pol I, buffers and nucleotides.

Applying that Court and MPEP sanctioned standard to the kit subject matter of claim 35, the kit provides a new and unobvious functional relationship between suramin and the printed instructions. That is, the printed instructions inform the user that a patient must have a low dose of circulating suramin (< 200 μM) over the duration of 48 hours. More important, the printed instructions provide an algorithm and the associated nomogram table for the physician or pharmacist to use to calculate the proper dose of non-cytotoxic suramin for each patient based on criteria not taught by Agyin, Tu, Klohs, or any other reference.

As discussed under "Summary of the Claimed Subject Matter", Appellants' disclosure of the nomogram is based on unexpected and surprising findings made after substantial experimentations in experimental animals and in human patients. Furthermore, the unusual and unexpected pharmacokinetic behaviors of non-cytotoxic suramin in humans are such that simple repetitive experimentation in the art will not be able to individualize the dose for a patient. These findings, in view of the multiple sources of inter-patient variability, mean that, absent the dosing nomogram in the instant disclosure, it will be *impossible* to predict how an individual patient will react to the administered dose of suramin and it would be *impossible* to calculate the correct dose based on the art of dose calculation for other drugs or cytotoxic suramin. The nomogram disclosed in the printed instructions is a novel method developed after extensive research undertaken to overcome or correct the deficiencies or misunderstanding in the art. The results of this research reveal the new, unexpected and unobvious requirements for finding the correct dose in individual patients. The nomogram accounts for the most critical variables in individual patients and enables the calculation of the personalized non-cytotoxic suramin dose in accordance to the patient's characteristics, such that 94% of the treatments administered to patients yielded circulating suramin concentration within the desired target range. This high success rate is surprising in view of the substantial inter-patient variability (180%) in the elimination of non-cytotoxic suramin in human patients, and underscores the utility and importance of the nomogram. Since the sensitization only works in a narrow concentration range, administration by an incorrect method can easily result in suramin concentrations that are too high and cause the loss of sensitization, or suramin concentrations that are too low and do not have a sensitizing effect. Hence, the ability to use non-cytotoxic suramin as a sensitizer in patients relies on using the printed instructions or nomogram for dose calculation. The substrate suramin in the kit cannot be used to provide a personalized treatment to a patient in accordance to said patient's characteristics without the printed matter. Likewise, the intended use of the printed instruction, *i.e.*, calculating the suramin dose to be given to a patient in accordance to said patient's personal characteristics, can only be practiced when the suramin is contained in the same kit.

Furthermore, absent the use of non-cytotoxic suramin as a sensitizer, suramin will have no therapeutic utility due to its lack of activity in human patients as a cytotoxic agent. The nomogram disclosed in the instant application is a simple and practical way to enable the use of non-cytotoxic suramin as a sensitizer. As such, the nomogram in effect is transforming suramin from a compound with no therapeutic value to a potentially useful drug.

Hence, Appellants respectfully submit that the nomogram breathes life and meaning into the kit, and that the requirement of a new and unobvious functional relationship between the printed instructions and the substrate has been met in the kit disclosed in claim 35.

The printed instructions represent new and unobvious findings that cannot be anticipated based on the art on dose-calculation of cytotoxic suramin or other drugs. Appellants respectfully draw the Board's attention to the surprising features and nonobviousness of the nomogram stated above under "Summary of the Claimed Subject Matter", in the section with the same heading. It is noted that the Examiner appears to agree that the nomogram method is new and unobvious, as he states: "While Applicants may very well have discovered a novel, unobvious way of determining suitable doses of suramin to administer to a patient,..." (April 19, 2010 Office Action, p. 5, second paragraph).

Examiner's statements 5 and 8 relate to the prior art of Agyin, Tu, and Klohs.
Appellants' response:

Appellants respectfully disagree that Agyin discloses a kit with suramin, instructions, and another chemotherapeutic, and that if even Agyin is interpreted as having disclosed such kit and instructions, the teaching of Agyin would not render the current disclosure of a kit obvious. Appellants' reasoning is as follows. Briefly, Agyin discloses pharmaceutical kits and, due to the broad description of kits in Agyin, such kits could even contain suramin. However, the kit of the instant disclosure is not obvious over Agyin, as the printed matter, including the dosing nomogram, is functionally related to the substrate of the kit (suramin), and has a new and unobvious relationship to the substrate. In contrast, Agyin lacks the novelty of the printed matter, as the instructions would present the dosing according to methods of the art known at the time of the invention.

In levying the final rejection of the appealed claims, the Examiner has stated, *inter alia*:

> Agyin et al. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 22 (col. 17, lines 56-57).
>
> January 5, 2009 Office action, p. 4 third paragraph.

Appellants respectfully disagree with the final rejection, because, as explained below, Agyin does not teach a suramin combination, and does not teach suramin as a potentiator.

Therefore, Agyin does not teach the appealed claim 35 and by definition all claims dependent therefrom.

First, none of Agyin's compounds have antitumor activity in animals bearing transplanted tumors. Agyin provided limited data to support enablement for the treatment of cancers. Cytotoxicity data was presented for 43 benzimidazole compounds and showed IC_{50} concentrations ranging from <10 nM (3 compounds), to >100 μM (6 compounds) (table 4), but none of the compounds tested showed *in vivo* antitumor effect at the highest dose tested (Table 6). As indicated in column 27, line 21, a treatment that causes an increase in lifespan of less than 25% (T/C<125%) is defined as a no activity treatment. All compounds tested showed no activity, except for compound 3-1, which has a T/C value of 132% in one of the four dose levels tested, *i.e.*, 50 mg/kg i.p. However, the other three dose levels, including a higher dose level of 100 mg/kg,i.p., showed inactive T/C values of 97%, 98%, and 108%. No enablement of combinations of benzimidazole compounds with other compounds, such as chemotherapeutic agents or "potentiators", was provided. It is generally known that drugs, which show activity in cultured tumor cells *in vitro*, frequently do not have antitumor activity in animals or human patients. It also is well known that compounds, which are inactive in animal models, are unlikely to be active in human patients. Furthermore, it is unlikely to receive regulatory approval for testing a drug that is without activity in animal models in humans. Therefore, an artisan will not be motivated to use the compounds of Agyin's invention, either singly or in combination, and Agyin does not teach the use of any form of combination therapy.

Second, Agyin does not teach a suramin combination. Agyin proposes to use the benzimidazoles in combination with any chemotherapy agent (column 12, ll. 51-54: "Chemotherapeutic agents used in combination with a compound of the present invention or salt thereof may be selected from any of these groups but are not limited thereto."), or with chemotherapeutic agents and/or potentiators (column 23, ll. 29-32), listing at least 91 compounds as possible "potentiators" (column 17, ll. 1-64). One of the listed compounds is suramin. The number of possible combinations proposed by Agyin, then, is at least (43 * >100 * >91 =) >391,300, where 43 is the number of presented benzimidazole compounds, >100 is the number of chemotherapeutic agents, and >91 is the number of "potentiators" listed. Agyin does not provide the rationale for choosing one combination over the other 390,000+ combinations. Hence, Agyin's proposal to use benzimidazole combinations is merely an invitation to the artisan to search for a possible effective combination from among more than 390,000 possibilities. Accordingly, an artisan would not know which of the >390,000 combinations to study. Even with the teaching of using carboplatin as the cytotoxic to be combined with any one of the 91 potentiators and any one of the 43 benzimidazole compounds, the number of possible

combinations is still >3,913, which is still a daunting number that would require substantial and burdensome experimentation.

Furthermore, it is well known in the art that there is only a vanishingly small chance of finding a synergistic drug combination, if the search process is a simple random testing of combinations of agents. Hence, an artisan would not be motivated to randomly test combinations. In short, Agyin's disclosure lacks specific and functional steps to enable an artisan to practice Agyin's invention. In fact, an artisan would be **discouraged** in using Agyin's teaching, since (a) the benzimidazole compounds are inactive in animal studies, (b) no data on possible synergy of any of the combinations is provided, and (c) no other indicators or rationales suggesting a beneficial effect of a combination with benzimidazole compounds were provided. Finally, since Agyin does not teach any combination, he also does not teach a particular combination containing suramin.

Third, Agyin does not teach using non-cytotoxic suramin as a potentiator for at least two reasons. First, Appellants have shown that the potentiator effect of suramin happens only at low concentrations (U.S. Patent No. 6,599,912). Suramin does **not** have sensitization effect at high dose. This shows that the dose is critical to enablement of using suramin. Because Agyin failed to provide the important enablement of the dose requirement, he does not teach using suramin as a potentiator. In addition, Agyin does not teach how to obtain the narrow concentration range of 10 to 50 μM maintained over 48 hours that would offer the sensitization effect. As described in the appealed application, development of the nomogram for finding the proper suramin dose required many innovative steps and extensive research including experimentation in human patients. Hence, a person with ordinary skills would not be able to combine suramin with the benzimidazole compounds.

The Examiner states (page 4, third ¶): "With regard to claim 26....". As claim 26 has been cancelled, this matter is moot.

Finally, Agyin does not teach using kits containing combinations of agents. The Examiner proposes that Agyin's teaching of possible combinations of chemotherapeutic agents and potentiators with anti-microtubule compounds of the appealed claims would make the kit of claim 26 obvious to one skilled in the art at the time the invention was made. Appellants respectfully disagree for several reasons. Agyin does not propose kits containing combinations of agents (column 24, ll. 6-22; claim 14). He only proposes kits containing a therapeutically effective amount of a benzimidazole. All other components of the kit are optional, and the list of optional components does not include chemotherapeutic agents or potentiators. Therefore, Agyin does **not** teach kits containing combinations of agents, and certainly not a kit containing a chemotherapeutic agent, non-cytotoxic suramin, and the instructions as needed to make

suramin effective as sensitizer or potentiator of the action of the chemotherapeutic agent. In addition, the instant disclosure is a nomogram that is required to enable the use of the kit containing suramin, which is used to improve the activity of one or more cytotoxic agents. The inventive element of instructions that enable application of medicaments, and that provide a functional relationship between the printed matter (instructions) and the claimed kit, is totally lacking in Agyin. His disclosure pertains to a number of compounds of which the utility has not been clearly proven, in spite of his claims that they are effective in the treatment of various diseases. In the remainder of his disclosure, he merely postulates that the utility of his compounds could be increased when used in combination with other compounds. This speculation appears grounded in the widely accepted rule in treatment development for cancer and viral diseases that the most effective therapies for these diseases frequently are combination therapies. This postulated utility, however, in no way anticipates the utility of the nomogram developed for the use of suramin as a sensitizer in the treatment of patients with cancer, and the utility of kits containing the nomogram, suramin, and the chemotherapeutic. As a result, Agyin does not render the appealed claims obvious.

Claims 27, 28, 32, 34 and 35 also are rejected as the targeted plasma suramin concentration of below 200 μM has been anticipated by Tu, Klohs, *or* Lopez. The Court's attention is drawn to a number of differences between this prior art and the personalized dosing nomogram in the instant disclosure, stated in "Summary of the Claimed Subject Matter", in the section under the heading "The printed instructions represent new and unobvious findings that cannot be anticipated based on the art regarding dose-calculation of cytotoxic suramin or other drugs". These multiple and significant differences make it impossible to use the methods developed by Tu and Klohs to calculate the dose of cytotoxic suramin.

Second, Tu, Klohs or Lopez does not teach the personalized dosing nomogram or the equations of claim 35.

Third, Tu and Klohs teach the use of suramin as a cytotoxic agent at the maximally tolerated doses that produce toxicity, *e.g.*, hematologic and gastrointestinal toxicity, in patients (plasma or serum concentration of over 100 μg/ml). For example, Tu describes using suramin at doses that produced the maximum tolerated steady state plasma concentration of 150-200 μg/ml, maintained for up to 45 weeks, when combined with doxorubicin. The Tu method yielded suramin levels that cause appreciable toxicity in patients. The Tu study shows "(s)ide effects similar to those reported for suramin and doxorubicin administered as individual agents were observed. Dose-limiting motor neuropathy developed in three patients (13%)." (Abstract). "The most common side effects were mucositis, hand and foot syndrome, and neutropenia..... It was

noteworthy that sensory neuropathy in the hands and feet caused by suramin therapy was masked by hand and foot syndrome caused by the weekly doxorubicin treatments. Furthermore, dysgeusia, as characterized by a metallic taste that lasted for months following the discontinuation of treatment, probably contributed to weight loss in some patients….. Coagulopathy occurred in one patient." (Discussion, page 1199 Column 2 third paragraph).

Klohs states, *inter alia*:

> Ideally, suramin will be administered at a dose which will produce plasma levels of about 100 to about 300 μg/ml. Suramin typically is administered by intravenous infusion over a 12- to 16-week period, as needed to maintain the indicated plasma levels. Suramin will be administered at about the same dose levels and frequency according to this invention.
>
> Klohs @ col. 2, ll. 34-38.

Hence, both Tu and Klohs are teaching the artisan to maintain the noted high and cytotoxic plasma levels (*viz.*, 100 to 300 μg/ml) for an extended time period of, *e.g.*, 12 to 16 weeks. To the contrary, Appellants have demonstrated that such high suramin concentration will not produce sensitization and teach away from using such cytotoxic suramin dose (see p. 3 ll 10- 24).

Lopez teaches using suramin in a culture flask and does not teach the determination of the suramin dose in a subject.

In contrast, the appealed application teaches the determination of the suramin dose that would yield and maintain low and non-cytotoxic plasma concentrations of 90 μg/ml or less for the duration of presence of effective chemotherapy concentrations, *e.g.*, 48 hours. As discussed under "Summary of the Claimed Subject Matter", in the section with the heading of "(T)he printed instructions represent new and unobvious findings that cannot be anticipated based on the art regarding dose-calculation of cytotoxic suramin or other drugs", the methods applied in the prior art for cytotoxic suramin cannot be used to determine the suramin dose needed for personalizing the non-cytotoxic suramin treatment in a patient according to said patient's characteristics.

Fourth, neither Tu nor Klohs contains the enablement steps to determine the suramin dose that would yield the targeted plasma concentrations effective for producing sensitization. For example, Tu describes the method of suramin dose determination as follows:

> Suramin was delivered iv over 2 h on Mondays and/or Thursdays. All patients received a test dose of 200 mg of suramin followed by a loading dose of 1 g/m^2. Subsequent suramin boluses were based on suramin concentrations measured 24 h after the previous infusion of the drug (i.e. on Tuesdays and Fridays).

> Suramin doses were estimated manually by the treating physician after a loading dose and two additional doses had been administered. Suramin doses were adjusted proportionately based on the assessment of Cpss.
>
> Tu @ p. 1194, under "Treatment Plan".

This instruction is not enabling, as it is unclear in its meaning. The required dose is "estimated manually", but the method of estimation is not detailed, as the meaning of "assessment of Cpss" is uncertain. For example, is the Cpss assumed to be equal to the plasma concentration measured one day after the last administered dose? Or is continuous accumulation of suramin concentrations taken into account? Due to the unusually long half-life of suramin ranging from greater than 11 days to as long as 78 days (see instant application, Table 3), achievement of steady-state concentrations is not expected after "a loading dose and two additional doses", or approximately 7 days at the biweekly dosing schedule. The standard assumption in clinical pharmacokinetics is that 3-4 half-lives are required to approach steady state, which would be at least 33 days for suramin. If the continuous accumulation of suramin concentrations is taken into account, is a one-compartment pharmacokinetic model assumed, or a two-compartment or a three-compartment model? Since all these factors have not been discussed, the methodology is unclear and not enabling.

Fifth, the method of Tu requires using a test dose in a patient in conjunction with repeated plasma sampling and real time drug concentration analyses for approximately 7 days, in order to calculate the dose that is eventually given to the same said patient. Clearly, then, the method of Tu requires delaying the first drug treatment until the concentration analyses are completed. In contrast, the appealed application does not require the use of a test dose and can be used to instantaneously determine the first treatment dose.

Sixth, the method of Tu requires concentration analysis of suramin in blood samples of the patient. In contrast, the nomogram does not require analyzing the suramin concentration in multiple blood samples from a patient in order to calculate the dose. The nomogram disclosed in the instant application is a simple and practical way to calculate a personalized suramin dose in individual patients based on the easily obtained patient characteristics, such as, squared value of said patient's body surface area and said patient's treatment time status.

Seventh, the prior art does not offer personalized treatment based on the treatment time status of an individual patient, which, as discussed throughout this document, is required to use the substrate in the instant kit to achieve its intended therapeutic purpose. In contrast, the instant disclosure accommodates changes in dosing intervals, a frequent necessity in clinical practice.

Examiner's statement 9 relates to "(T)here is no support, either explicit or implicit, for the claimed amount of suramin. Nowhere do Applicants teach the claimed limitation of an amount of suramin "not substantially in excess of about 800 mg".

Appellants' Response:

Appellants draw the Court's attention to Claim 22 in the original application, which states:

Claim 22. A kit for carrying out the combined administration of suramin with one or more cytotoxic agents, comprising:

(a) suramin formulated in a pharmaceutical carrier; and

(b) instructions for therapeutic use of said suramin in combination with said cytotoxic agent(s) in one or more of inhibiting growth, proliferation of tumor cells, or inducing killing of tumor cells, calling for:

(i) administering suramin, if required, in a required dose to establish a low circulating concentration of suramin in said patient of below about 200 μM; and

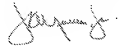
(ii) administering said chemotherapeutic agent to said patient when said low circulating concentration of suramin of below about 200 μM is present in said patient.

Based on the above disclosure, in view of the demonstration that the dose of suramin can be calculated using the nomogram provided in the kit, the instant application has provided support for the amount of suramin in the kit. For example, the first dose of suramin is the largest dose, and is 125 *(BSA squared), as given in the nomogram of Claim 35. It is well-known in the art that the average patient has a body surface area of about 1.7 m^2. Allowing for about 50% increase for larger patients to 2.5 m^2, the required dose would be 125*(squared value of 2.5) or 781 mg. A vial of suramin containing up to 800 mg would then be a logical choice.

Conclusion

Accordingly, Appellants respectfully urge the Court to overrule the rejection of the appealed claims and to permit the appealed application to pass to issue.

Respectfully submitted,



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CLAIMS APPENDIX

The Appealed Claims

Claim 27. The kit of claim 35, wherein the resulting circulating plasma concentration of suramin in said patient is between about 10 and 200 μM.

Claim 28. The kit of claim 27, the resulting circulating plasma concentration of suramin in said patient is between about 10 and 50 μM.

Claim 32. The kit of claim 27, wherein said nomogram results in a patient circulating concentration of suramin of between about 10 to about 50 μM over 48 hours.

Claim 33. The kit of claim 35, wherein two-thirds of the calculated individual dose of suramin for each treatment is given on the first day and the remaining one-third of the calculated individual dose is given about 24 hours later.

Claim 35. A kit for providing individual treatment of suramin to a patient, comprising:

(a) not substantially in excess of about 800 mg of suramin formulated in a pharmaceutical carrier; and

(b) a dosing nomogram to calculate the dose of suramin for a patient based on the body surface area and the timing of the treatment for said patient, whereby the dose is calculated as the multiplication product of (squared value of said patient's body surface area or BSA) and (numerical value of a factor or FACTOR), in accordance to the following table; said calculation comprising:

(b1) calculating the first treatment dose as the multiplication product of (squared value of said patient's BSA) and (125); and

(b2) calculating the second and subsequent doses as the multiplication product of (squared value of said patient's BSA) and (numerical value of FACTOR), wherein FACTOR is determined by the elapsed days since last suramin treatment

said nomogram table comprising:

Nomogram For Calculating Suramin Dose

Cycle 1*	125
Second and subsequent treatments use different values of FACTOR in accordance with	FACTOR

patient's time of treatment, expressed as elapsed time (in days) since the start of the previous treatment	
7	39
8	43
9	47
10	51
11	55
12	58
13	61
14	64
15	67
16	69
17	72
18	74
19	76
20	78
21	80
22	82
23	84
24	86
25	87
26	88
27	90
28	91
29	92
30	93
31	94

32	95
33	96
34	97
35	98
36	98
37	99
38	100
39	100
41	102
42	102
44	103
47	104
49	105
52	106
55	106

and whereby the dose for elapsed times not included in the nomogram table, being less than 7 days or more than 55 days, is calculated in accordance to the following equation:

Subsequent cycle dose (mg) = First dose * $(1- e^{-k \cdot t}) = 125*BSA^{2}*(1- e^{-k \cdot t})$ Eq. 16

wherein

"BSA" is body surface area in units of m^2,

"BSA^{2}" is the squared value of BSA and is entered as a unitless value,

"k" is the rate constant of decline of suramin concentrations in plasma in units of 1/hour, and is 0.0026 1/hour,

"t" is time after suramin administration in units of hours.

EVIDENCE APPENDIX

March 6, 2008 Declaration of Jessie L.-S. Au

RELATED PROCEEDINGS APPENDIX

None.